Remarks

Claims 1, 5-9, 14, 20, 22-25, 27, 29, 31-33, 35-39, 41, 42, 44-49, 51-53, 55-59, 69, and 70 are pending. Claims 1, 24, and 53 have been amended. Claims 11-13, 15, and 21 are canceled herein. Claims 69 and 70 are newly added.

Claim 1 was amended to recite rolling circle replication of the ATC by extension of the P1 primers to form multiple TS-DNA products. Support for rolling circle replication of the ATC by extension of the P1 primers can be found at least in Figure 1 as well as on page 15, lines 24-28 where the initial round of rolling circle amplification is described. Claim 1 was also amended to recited that the amplification target circles are single stranded. Support for this can be found at least in original claim 11. Claim 24 was amended to be consistent with amended claim 1. Claim 53 was amended to correct a typographical error.

New claim 69 recites that conditions that promote rolling circle replication of are isothermic conditions. Support for isothermic conditions can be found at least on page 3, lines 10-13 where isothermic conditions are described for amplification of single-stranded or double-stranded circular target DNA molecules.

New claim 70 recites that each ATC hybridizes simultaneously to a plurality of said P1 primers. Support for simultaneous hybridization can be found at least on page 6, lines 2-9 where multiple extensions of P1 primers are achieved simultaneously from a single amplification target circle.

Rejections Under 35 USC § 103

1. Claims 1, 5-9, 11, 13, 15, 20-25, 27, 29, 31, 33, 35, 38, 39, 41, 44-49, 51-53, 55 and 56 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi (U.S. Patent No. 5,854,033), Landers et al. (U.S. Patent No. 6,703,228), and Eckstein et al. (Trends in Bioch. Sci., vol. 14(3), pp. 97-100, 1989). Applicant respectfully traverses this rejection to the extent it is applied to the claims as amended.

Lizardi discloses a method of rolling circle amplification (RCA) involving replication of single-stranded DNA molecules (see column 19, lines 21-23). Lizardi discloses use of a rolling circle replication primer of defined sequence that hybridizes to an amplification target circle

(ATC) followed by rolling circle replication of the ATC primed by the rolling circle replication primer to produce a tandem sequence DNA (see column 19, lines 20-31). Lizardi fails to disclose or suggest the use of primers having random sequence, fails to disclose or suggest hybridization of a plurality of primers to each amplification target circle and fails to disclose or suggest formation of multiple tandem sequence DNA products by extension of multiple primers.

Landers et al. discloses a PCR method of genotyping referred to as arbitrarily primed PCR (AP-PCR) (see column 17, lines 28-29). AP-PCR utilizes short oligonucleotides with arbitrary sequences as PCR primers to amplify a discrete subset of portions of a high complexity genome (see column 17, lines 28-33 of Landers et al.).

Eckstein et al. discloses nuclease resistant primers.

Claims 1, 5-9, 20, 22-25, 27, 29, 31, 33, 35, 38, 39, 41, 44-49, 51-53, 55 and 56 involve contacting multiple single stranded non-circular random oligonucleotide primers (P1) and one or more single stranded amplification target circles, where each ATC hybridizes to a plurality of the P1 primers, under conditions that promote rolling circle replication of the amplification target circle by extension of the P1 primers to form multiple tandem sequence DNA (TS-DNA) products. At least one dNTP renders the TS-DNA resistant to nuclease activity following incorporation into the TS-DNA. Thus the claims require use of single stranded amplification target circles, hybridization of a plurality of P1 primers of random sequence to each ATC under conditions that promote rolling circle replication of the ATC by extension of the P1 primers to form multiple TS-DNA products by extension of the P1 primers.

In making a determination of obviousness under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that (1) the prior art suggests the invention developed, and (2) the prior art indicates that the invention would have a reasonable likelihood of success. *See In re Dow Chem. Co.*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988); *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987). In order for a reference to be effective prior art under 35 U.S.C. § 103, it must provide a motivation whereby one of ordinary skill in the art would be led to do that which the applicant has done. *See Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). The Patent Office has the burden under § 103 to

establish a *prima facie* case of obviousness, which can be satisfied only by showing some objective teaching in the prior art would lead one to combine the relevant teachings of the references. *See In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988).

The Cited Publications Do Not Disclose or Suggest Use of Random Primers in Rolling Circle Replication

The present claims require the use of random primers for priming rolling circle replication of single stranded amplification target circles. The Office Action alleges (page 9, lines 5-7) that it would have been *prima facie* obvious to one of ordinary skill in the art to have included the PCR primers of arbitrary sequence and high complexity genomes of Landers et al. in the method of Lizardi. The Office Action argues that those of skill in the art would have been motivated to do so because Landers et al. allegedly provides that random primers allow amplification of unknown DNA sequences and that using double stranded DNA allowed for reducing complexity of genomic samples. Applicants disagree that Landers et al. either suggests that primers of random sequence could or should be used for rolling circle replication of single stranded circles or provides motivation for such a substitution.

First, none of Landers et al., Lizardi or Eckstein et al. suggest the use of primers of random sequence in the method of Lizardi. Second, there is no motivation apparent from the cited publications to substitute the random primers of Landers et al. for the defined primers of Lizardi. To avoid the impermissible error of hindsight reconstruction, a specific and direct suggestion or motivation to alter the prior art to arrive at applicants invention must be present or apparent from the prior art; it cannot be merely a conclusion of the examiner. In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) (to reject an inventor's claim for obviousness in view of a combination of prior art references, a showing of a suggestion, teaching, or motivation must be "clear and particular."). Although Landers et al. discusses reasons for using primers of random sequence for PCR amplification, there is no indication in Landers et al. that such reasons apply to rolling circle replication amplification. Neither Lizardi nor Eckstein et al. provide any disclosure or suggestion for the use of random primers. In fact, Lizardi focuses on specific replication of amplification target circles to the exclusion of other

sequences that may be present. For example, Lizardi notes (column 6, lines 51-52) that each open circle probe should have a single primer complement portion.

Landers et al. is solely concerned with PCR amplification of highly complex genomic DNA samples. The only circular targets of such PCR amplification disclosed by Landers et al. are double stranded yeast artificial chromosomes (YACs; column 17, lines 60-66). Significantly, Landers et al. does not even identify the YACs as being circular (and thus Landers et al. cannot provide any general suggestion to use random primers on circular templates). The vast majority of genomic DNA to be amplified in the method of Landers et al. is linear double stranded DNA.

PCR, the amplification technique of Landers et al., is fundamentally different from the rolling circle replication method of Lizardi. Lizardi notes (column 3, lines 24-31) that the rolling circle replication method there allows target sequences to be amplified via a small diagnostic probe with a defined primer of arbitrary sequence, allowing consistency in the priming and replication reactions, even between probes having very different target sequences. Lizardi also notes (column 3, lines 31-34) that amplification takes place not in cycles, but in continuous, isothermal replication (rolling circle replication), making amplification less complicated and much more consistent in output. Thus, the rolling circle method of Lizardi solves the problem of replication of target sequences in a very different way than the PCR method of Landers et al. None of Landers et al., Lizardi or Eckstein et al. provide any indication that primers of random sequence should or could be used in a rolling circle replication method. This is not enough to satisfy the burden on the Patent Office to find direct motivation in the cited prior art. Accordingly, for at least these reasons, the cited publications fail to establish a prima facie case of obviousness.

The Cited Publications Do Not Disclose or Suggest Use of Multiple Primers Priming Rolling Circle Replication from a Single Circular Template

The present claims require that each amplification target circle hybridize to a plurality of P1 primers and that multiple tandem sequence DNA products be produced by extension of the P1 primers in rolling circle replication. Neither Landers et al. nor Eckstein et al. discuss rolling circle replication and thus do not disclose or suggest use of multiple priming of rolling circle

replication of a single circular template. Lizardi describes methods of rolling circle replication but fails to specifically disclose or suggest that an amplification target circle hybridize to a plurality of primers such that multiple tandem sequence DNA products are produced. Thus, it is not obvious from the cited publications, taken either alone or in combination, to hybridize each amplification target circle to a plurality of primers such that multiple tandem sequence DNA products be produced by extension of the primers in rolling circle replication.

While it is true that the methods of Lizardi generically encompass the use of multiple primers and that in some embodiments of the methods of Lizardi the use of rolling circle replication primers and tertiary DNA strand displacement primers together might result more than one primer hybridizing to a single amplification target circle, Lizardi does not specifically disclose and certainly does not suggest the use of multiple rolling circle replication primers nor formation of multiple tandem sequence DNA products from multiple primings of a single amplification target circle. It is clear that the mere fact that certain subject matter is disclosed within a broader generic disclosure does not make obvious the specific subjected matter not specifically disclosed. In re Baird, 16 F.3d 380, 382, 29 USPQ2d 1550 (Fed. Cir. 1994). Neither Landers et al. nor Eckstein et al. provide any disclosure or suggestion regarding rolling circle replication and thus do not provide any suggestion to focus the method of Lizardi on the claimed use of multiple primers and multiple primings.

For at least these reasons, Lizardi, Landers et al. and Eckstein et al., either alone or in combination, fail to make obvious claims 1, 5-9, 11, 13, 15, 20-25, 27, 29, 31, 33, 35, 38, 39, 41, 44-49, 51-53, 55 and 56. As such, Applicant respectfully requests withdrawal of this rejection.

2. Claims 12, 36 and 37 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi (U.S. Patent No. 5,854,033), Landers et al. (U.S. Patent No. 6,703,228), and Eckstein et al. (Trends in Bioch. Sci., vol. 14(3), pp. 97-100, 1989) and in further view of Rothberg et al. (U.S. Patent No. 6,274,320). Applicant respectfully traverses this rejection to the extent it is applied to the claims as amended.

Claims 12, 36 and 37 depend from claim 1 and therefore encompass all the limitations of claim 1. Applicant notes that the rejection applies Lizardi, Landers et al., and Eckstein et al. in

the same way and for the same disclosure for which Lizardi, Landers et al., and Eckstein et al. were applied in the rejection of claims 1, 5-9, 11, 13, 15, 20-25, 27, 29, 31, 33, 35, 38, 39, 41, 44-49, 51-53, 55 and 56 under 35 U.S.C. § 103(a) discussed above. As discussed above, Lizardi, Landers et al., and Eckstein et al., either alone or in combination, fail to disclose, suggest, or provide motivation for the use of primers of random sequence in the method of Lizardi or hybridization of each amplification target circle to a plurality of primers such that multiple tandem sequence DNA products be produced by extension of the primers in rolling circle replication. Rothberg et al. fails to supplement this gap in Lizardi, Landers et al., and Eckstein et al.

Rothberg et al. was cited for disclosure of amplification of circular templates by rolling circle amplification primers attached to a solid support where the solid supports being a DNA chip or a glass slide or an optical fiber. This does not supply what is missing from Lizardi, Landers et al., and Eckstein et al. Thus, Lizardi, Landers et al., Eckstein et al., and Rothberg et al., either alone or in combination, fail to disclose, suggest, or provide motivation for the use of primers of random sequence in the method of Lizardi or hybridization of each amplification target circle to a plurality of primers such that multiple tandem sequence DNA products be produced by extension of the primers in rolling circle replication. Accordingly, Lizardi, Landers et al., Eckstein et al., and Rothberg et al. fail to make obvious claims 12, 36 and 37. Applicant respectfully requests withdrawal of this rejection.

3. Claims 14, 57 and 58 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi (U.S. Patent No. 5,854,033), Landers et al. (U.S. Patent No. 6,703,228), and Eckstein et al. (Trends in Bioch. Sci., vol. 14(3), pp. 97-100, 1989) and in further view of Navarro et al. (J. Virol. Meth., vol. 56, pp. 59-66, 1996). Applicant respectfully traverses this rejection to the extent it is applied to the claims as amended.

Claims 14, 57 and 58 depend from claim 1 and therefore encompass all the limitations of claim 1. Applicant notes that the rejection applies Lizardi, Landers et al., and Eckstein et al. in the same way and for the same disclosure for which Lizardi, Landers et al., and Eckstein et al. were applied in the rejection of claims 1, 5-9, 11, 13, 15, 20-25, 27, 29, 31, 33, 35, 38, 39, 41,

44-49, 51-53, 55 and 56 under 35 U.S.C. § 103(a) discussed above. As discussed above, Lizardi, Landers et al., and Eckstein et al., either alone or in combination, fail to disclose, suggest, or provide motivation for the use of primers of random sequence in the method of Lizardi or hybridization of each amplification target circle to a plurality of primers such that multiple tandem sequence DNA products be produced by extension of the primers in rolling circle replication. Navarro et al. fails to supplement this gap in Lizardi, Landers et al., and Eckstein et al.

Navarro et al. was cited for disclosure of amplification of circular RNA viroids using random hexamers and AMV reverse transcriptase. This does not supply what is missing from Lizardi, Landers et al., and Eckstein et al. Thus, Lizardi, Landers et al., Eckstein et al., and Novarro et al., either alone or in combination, fail to disclose, suggest, or provide motivation for the use of primers of random sequence in the method of Lizardi or hybridization of each amplification target circle to a plurality of primers such that multiple tandem sequence DNA products be produced by extension of the primers in rolling circle replication. Accordingly, Lizardi, Landers et al., Eckstein et al., and Novarro et al. fail to make obvious claims 14, 57 and 58. Applicant respectfully requests withdrawal of this rejection.

4. Claims 32, 42 and 59 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi (U.S. Patent No. 5,854,033), Landers et al. (U.S. Patent No. 6,703,228), and Eckstein et al. (Trends in Bioch. Sci., vol. 14(3), pp. 97-100, 1989) and in further view of Skerra et al. (Nucleic Acid research, Vol. 20, pp. 3551-3554, 1992). Applicant respectfully traverses this rejection to the extent it is applied to the claims as amended.

Claims 32, 42 and 59 depend from claim 1 and therefore encompass all the limitations of claim 1. Applicant notes that the rejection applies Lizardi, Landers et al., and Eckstein et al. in the same way and for the same disclosure for which Lizardi, Landers et al., and Eckstein et al. were applied in the rejection of claims 1, 5-9, 11, 13, 15, 20-25, 27, 29, 31, 33, 35, 38, 39, 41, 44-49, 51-53, 55 and 56 under 35 U.S.C. § 103(a) discussed above. As discussed above, Lizardi, Landers et al., and Eckstein et al., either alone or in combination, fail to disclose, suggest, or provide motivation for the use of primers of random sequence in the method of Lizardi or

hybridization of each amplification target circle to a plurality of primers such that multiple tandem sequence DNA products be produced by extension of the primers in rolling circle replication. Skerra et al. fails to supplement this gap in Lizardi, Landers et al., and Eckstein et al.

Skerra et al. was cited for disclosure of incorporation of a phosphorothioate nucleotide at the 3'-end of the primer renders it inactive to the 3'->5' exonuclease activity of DNA polymerases such as Vent and Pfu and use of a mixture of exonuclease-sensitive and exonuclease-resistant primers in the amplification reaction. This does not supply what is missing from Lizardi, Landers et al., and Eckstein et al. Thus, Lizardi, Landers et al., Eckstein et al., and Skerra et al., either alone or in combination, fail to disclose, suggest, or provide motivation for the use of primers of random sequence in the method of Lizardi or hybridization of each amplification target circle to a plurality of primers such that multiple tandem sequence DNA products be produced by extension of the primers in rolling circle replication. Accordingly, Lizardi, Landers et al., Eckstein et al., and Skerra et al. fail to make obvious claims 32, 42 and 59. Applicant respectfully requests withdrawal of this rejection.

Pursuant to the above remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

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Request for Continued Examination pursuant to 37 C.F.R. § 1.114 are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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